REMARKS

Applicant's Preliminary Amendment is submitted together with a divisional application directed to Claims 8, 13-16, 24, 28-36, 46-72, and 87-89, originally filed in pending parent U.S. Serial No. 09/399,212 filed September 17, 1999 which claims were designated Group II in a restriction requirement, mailed December 20, 2000.

Applicant believes that no new matter is introduced by any amendments made herein.

At page 1, line 3, Applicant has added continuing data explaining the relationship to U.S. Serial No. 09/399,212 filed September 17, 1999 and other related applications.

The cancellation of Claims 1-7, 9-12, 17-23, 25-27, 37-45, 73-86, and 90-108 without prejudice, is made because Claims 1-7, 9-12, 17-23, 25-27, 37-45, 73-86, and 90-108 were designated claim Groups I, III, IV and V, and are not directed to the subject matter of the present division (i.e., Group II).

Applicant's cancellation of Claims 8, 13-16, 24, 28-36, 46-72, and 87-89 is made without prejudice. New Claims 109-153 are added, and support is found, for example, in Claims 8, 13-16, 24, 28-36, 46-72, and 87-89 as originally filed.

In view of the above amendments and remarks, it is submitted that this application is now ready for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (213) 896-6665.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

At page 1, line 3, before "Field of the Invention", please insert the following:

--This application is a division of U.S. Serial No. 09/399,212 filed September 17, 1999, and is further related to U.S. Serial No. _____, filed July 2, 2001, which is a division of U.S. Serial No. 09/399,212.--.

IN THE CLAIMS:

Please cancel Claims 1-7, 9-12, 17-23, 25-27, 37-45, 73-86, and 90-108 without prejudice, as being directed to designated claim Groups I, III, IV and V, and are not directed to the subject matter of the present division (i.e., Group II). Please cancel Claims 8, 13-16, 24, 28-36, 46-72, and 87-89 without prejudice and add New Claims 109-153.

-- 109. (New) A *nucleic acid probe or primer comprising*:

(A) a nucleotide sequence of (SEQ. ID. NO.:1), a nucleotide sequence complementary thereto, a degenerate coding sequence thereof, or a gene-specific fragment of any of these; or

(B) a nucleic acid segment encoding a human PAPSS2 protein having an amino acid sequence of (SEQ. ID. NO.:7).

110. (New) The nucleic acid probe or primer of Claim 109, wherein the gene specific fragment has a nucleotide sequence comprising 5'-TGGACCAAGGATGACGATGT-3' (SEQ. ID. NO.: 3), a complementary nucleotide sequence, or a *PAPSS2*-specific sequence overlapping either of these at 5 or more contiguous nucleotides at its 5' or 3' end.

111. (New) The nucleic acid probe or primer of Claim 109, wherein the gene specific fragment has a nucleotide sequence comprising 5'-CGGAAAGATGGCAACAATGG

(SEQ. ID. NO.: 4), a complementary nucleotide sequence, or a *PAPSS2*-specific sequence overlapping either of these at 5 or more contiguous nucleotides at its 5' or 3' end.

112. (New) The nucleic acid construct of Claim 109, wherein the the gene specific fragment has a nucleotide sequence comprising 5'-CTGGTGCTGGAAAAACAACG-3' (SEQ. ID. NO.: 5), a complementary nucleotide sequence, or a *PAPSS2*-specific sequence overlapping either of these at 5 or more contiguous nucleotides at its 5' or 3' end.

113. (New) The nucleic acid construct of Claim 109, wherein the the gene specific fragment has a nucleotide sequence comprising 5'-TGCGAATGGAGAAATAAAGCTG (SEQ. ID. NO.: 6), a complementary nucleotide sequence, or a *PAPSS2*-specific sequence overlapping either of these at 5 or more contiguous nucleotides at its 5' or 3' end.

114. (New) A nucleic acid construct wherein the nucleic acid segment is a probe or primer, comprising:

(A) a nucleotide sequence of (SEQ. ID. NO.:2), a nucleotide sequence complementary thereto, a degenerate coding sequence thereof, or a gene-specific fragment of any of these; or

(B) a nucleic acid segment encoding a human PAPSS2 protein having an amino acid sequence of (SEQ. ID. NO.:8).

115. (New) An oligonucleotide primer for amplifying a *PAPSS2*-specific nucleic acid segment, comprising:

(A) (SEQ. ID. NO.:3), (SEQ. ID. NO.:4), (SEQ. ID. NO.:5), (SEQ. ID. NO.:6), (SEQ. ID. NO.:11), (SEQ. ID. NO.:12), (SEQ. ID. NO.:13), (SEQ. ID. NO.:14), (SEQ. ID. NO.:15), (SEQ. ID. NO.:16), (SEQ. ID. NO.:17), (SEQ. ID. NO.:18), or (SEQ. ID. NO.:28);

(B) a nucleotide sequence complementary to (A);

(C) a *PAPSS2*-specific fragment of (A) or (B) at least 15 nucleotides long; or

(D) a *PAPSS2*-specific nucleotide sequence overlapping at 5 or more contiguous nucleotide positions any sequence of (A) or (B) at its 5' or 3' end.

116. (New) An oligonucleotide primer for amplifying a *Papss2*-specific nucleic acid segment, comprising:

(A) (SEQ. ID. NO.:19), (SEQ. ID. NO.:20), (SEQ. ID. NO.:21), (SEQ. ID. NO.:22), (SEQ. ID. NO.:23), (SEQ. ID. NO.:24), (SEQ. ID. NO.:25), (SEQ. ID. NO.:26), or (SEQ. ID. NO.:27);

(B) a nucleotide sequence complementary to (A);

(C) a *Papss2*-specific fragment of (A) or (B) at least 15 nucleotides long; or

(D) a *Papss2*-specific nucleotide sequence overlapping at 5 or more contiguous nucleotide positions any sequence of (A) or (B) at its 5' or 3' end.

117. (New) A pair of oligonucleotide primers comprising a forward and a reverse primer, said pair capable of producing detectable nucleic acid amplification products having:

(A) (SEQ. ID. NO.:1) or (SEQ. ID. NO.:9);

(B) a nucleotide sequence complementary to (A); or

(C) a *PAPSS2* gene-specific fragment of (A) or (B).

118. (New) The pair of oligonucleotide primers of Claim 117, wherein

the forward primer has a nucleotide sequence comprising 5'-TGGACCAAGGATGACGATGT-3' (SEQ. ID. NO.: 3), a complementary nucleotide sequence, or a *PAPSS2*-specific fragment of either of these at least 15 nucleotides long; and

the reverse primer has a nucleotide sequence comprising 5'-CGGAAAGATGGCAACAATGG-3' (SEQ. ID. NO.: 4), a complementary nucleotide sequence, or a *PAPSS2*-specific fragment of either of these at least 15 nucleotides long.

119. (New) The pair of oligonucleotide primers of Claim 117, wherein

the forward primer has a nucleotide sequence comprising 5'-CTGGTGCTGGAAAAACAACG-3' (SEQ. ID. NO.: 5), a complementary sequence, or a *PAPSS2*-specific fragment of either at least 15 nucleotides long; and

the reverse primer has a nucleotide sequence comprising 5'-TGCGAATGGAGAAATA AAGCTG-3' (SEQ. ID. NO.: 6), a complementary sequence, or a *PAPSS2*-specific fragment of either at least 15 nucleotides long.

120. (New) The pair of oligonucleotide primers of Claim 117, wherein the forward primer comprises:

(A) (SEQ. ID. NO.:3), (SEQ. ID. NO.:5), (SEQ. ID. NO.:11), (SEQ. ID. NO.:12), or (SEQ. ID. NO.:13);

(B) a nucleotide sequence complementary to any of (A);

(C) a gene-specific fragment of (A) or (B) at least 15 nucleotides long; or

(D) a *PAPSS2*-specific nucleotide sequence overlapping at 5 or more contiguous nucleotide positions any sequence of (A) or (B) at its 5' or 3' end; and

a reverse primer comprising:

(E) (SEQ. ID. NO.:4),(SEQ. ID. NO.:6), (SEQ. ID. NO.:14), (SEQ. ID. NO.:15), (SEQ. ID. NO.:16), (SEQ. ID. NO.:17), or (SEQ. ID. NO.:18);

(F) a nucleotide sequence complementary to any of (E);

(G) a *PAPSS2*-specific fragment of (E) or (F) at least 15 nucleotides long; or

(H) a *PAPSS2*-specific nucleotide sequence overlapping at 5 or more contiguous nucleotide positions any sequence of (E) or (F) at its 5' or 3' end.

121. (New) A pair of oligonucleotide primers comprising a forward and a reverse primer, said pair capable of producing detectable nucleic acid amplification products having:

(A) (SEQ. ID. NO.:2) or (SEQ. ID. NO.:10);

(B) a nucleotide sequence complementary to (A); or

(C) a *Papss2* gene-specific fragment of (A) or (B).

122. (New) The pair of oligonucleotide primers of Claim 121, wherein the forward primer comprises:

(A) (SEQ. ID. NO.:20), (SEQ. ID. NO.:22), (SEQ. ID. NO.:23), or (SEQ. ID. NO.:27);

(B) a nucleotide sequence complementary to any of (A);

(C) a *Papss2*-specific fragment of (A) or (B) at least 15 nucleotides long; or

(D) a *Papss2*-specific nucleotide sequence overlapping at 5 or more contiguous nucleotide positions any sequence of (A) or (B) at its 5' or 3' end; and

the reverse primer comprises:

(E) (SEQ. ID. NO.:19), (SEQ. ID. NO.:21), (SEQ. ID. NO.:24), (SEQ. ID. NO.:25), or (SEQ. ID. NO.:26);

(F) a nucleotide sequence complementary to any of (E);

(G) a *Papss2*-specific fragment of (E) or (F) at least 15 nucleotides long; or

(H) a *Papss2*-specific nucleotide sequence overlapping at 5 or more contiguous nucleotide positions any sequence of (E) or (F) at its 5' or 3' end.

123. (New) The pair of oligonucleotide primers of Claim 121, wherein

the forward primer has a nucleotide sequence comprising (SEQ. ID. NO.:20), a complementary nucleotide sequence, a gene-specific fragment of either of these at least 15 nucleotides long; and

the reverse primer has a nucleotide sequence comprising (SEQ. ID. NO.:21), a complementary nucleotide sequence, or a gene-specific fragment of either of these at least 15 nucleotides long.

124. (New) A method of diagnosing spondyloepimetaphyseal dysplasia in a human subject, comprising:

a) amplifying a nucleic acid segment from a sample of a bodily substance containing human nucleic acid, said sample being derived from a human subject having at least one symptom of spondyloepimetaphyseal dysplasia, said nucleic acid segment defining a sequence from human chromosomal region 10q23-24, between microsatellite markers D10S1143 and D10S2470, to produce amplification products; and

b) analyzing the amplification products for the presence of homozygosity for a variant allele of a *PAPSS2* gene, the presence of homozygosity for the variant allele of the gene corroborating a diagnosis of spondyloepimetaphyseal dysplasia in the human subject.

125. (New) The method of Claim 124, wherein the sample is of blood, hair root, urine, amniotic fluid, spinal fluid, skin, vascular epithelium, oral epithelium, or chorionic villus.

126. (New) The method of Claim 124, wherein an oligonucleotide primer is used to amplify the nucleic acid segment.

127. (New) The method of Claim 126, wherein the oligonucleotide primer has a nucleotide sequence of 5'-TGGACCAAGGATGACGATGT-3' (SEQ. ID. NO.:3), 5'-CGGAAAGATGGCAACAATGG-3' (SEQ. ID. NO.:4), a sequence complementary to either, a *PAPSS2*-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or

more contiguous nucleotide positions of any of these at its 5' or 3' end, or a *PAPSS2*-specific fragment of any of these at least 15 nucleotides long.

128. (New) The method of Claim 126, wherein the oligonucleotide primer has a nucleotide sequence of 5'-CTGGTGCTGGAAAAACAACG-3' (SEQ. ID. NO.:5), 5'-TGCGAATGGAGAA ATAAAGCTG-3' (SEQ. ID. NO.:6), a sequence complementary to either, a *PAPSS2*-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or more contiguous nucleotide positions of any of these at its 5' or 3' end, or a *PAPSS2*-specific fragment of any of these at least 15 nucleotides long.

129. (New) The method of Claim 124, wherein the variant allele is characteristic of SEMD Pakistani-type.

130. (New) A method of diagnosing spondyloepimetaphyseal dysplasia Pakistani-type in a human subject, comprising:

a) amplifying a nucleic acid segment from a sample of a bodily substance containing human nucleic acid, said sample being derived from a human subject having at least one symptom of spondyloepimetaphyseal dysplasia Pakistani-type, said nucleic acid segment defining a sequence from human chromosomal region 10q23-24, between microsatellite markers D10S1143 and D10S2470, to produce amplification products; and

b) analyzing the amplification products for the presence of homozygosity for a variant allele of a gene encoding a PAPS synthetase, said variant allele defining a stop codon instead of a serine codon corresponding to amino acid residue 475 of SEQ. ID. NO.:7, the presence of homozygosity for the variant allele corroborating a diagnosis of spondyloepimetaphyseal dysplasia Pakistani-type in the human subject.

131. (New) The method of Claim 130, wherein the sample is of blood, hair root, urine, amniotic fluid, spinal fluid, skin, vascular epithelium, oral epithelium, or chorionic villus.

132. (New) The method of Claim 130, wherein an oligonucleotide primer is used to amplify the nucleic acid segment.

133. (New) The method of Claim 130, wherein the oligonucleotide primer has a nucleotide sequence of 5'-TGGACCAAGGATGACGATGT-3' (SEQ. ID. NO.:3), 5'-CGGAAAGATGGCAACAATGG-3' (SEQ. ID. NO.:4), a sequence complementary to either, a *PAPSS2*-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or more contiguous nucleotide positions of any of these at its 5' or 3' end, or a *PAPSS2*-specific fragment of any of these at least 15 nucleotides long.

134. (New) The method of Claim 130, wherein the oligonucleotide primer has a nucleotide sequence of 5'-CTGGTGCTGGAAAAACAACG-3' (SEQ. ID. NO.:5), 5'-TGCGAATGGAGAA ATAAAGCTG-3' (SEQ. ID. NO.:6), a sequence complementary to either, a *PAPSS2*-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or more contiguous nucleotide positions of any of these at its 5' or 3' end, or a *PAPSS2*-specific fragment of any of these at least 15 nucleotides long.

135. (New) A method of diagnosing spondyloepimetaphyseal dysplasia Pakistani-type in a human subject, comprising:

a) amplifying a nucleic acid segment from a sample of a bodily substance containing human nucleic acid, said sample being derived from a human subject having at least one symptom of spondyloepimetaphyseal dysplasia Pakistani-type, said nucleic acid segment defining a sequence from human chromosomal region 10q23-24, between microsatellite markers D10S1143 and D10S2470, to produce amplification products, using at least one oligonucleotide primer having a sequence that comprises (SEQ. ID. NO.: 3), (SEQ. ID. NO.:4), (SEQ. ID. NO.:5), (SEQ. ID. NO.:6), a sequence complementary to any of these, a *PAPSS2*-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or more contiguous nucleotide positions of any of these at its 5' or 3' end, or a *PAPSS2*-specific fragment of any of these at least 15 nucleotides long; and

b) analyzing the amplification products for the presence of homozygosity for a variant allele of a gene encoding a PAPS synthetase, said variant allele defining a stop codon instead of a serine codon corresponding to amino acid residue 475 of SEQ. ID. NO.:7, the presence of homozygosity for the variant allele corroborating a diagnosis of spondyloepimetaphyseal dysplasia Pakistani-type in the human subject.

136. (New) The method of Claim 135, wherein analyzing the amplification products comprises digesting the amplification products with a *Hinc* II restriction endonuclease.

137. (New) The method of Claim 135, wherein the sample is blood, hair root, urine, amniotic fluid, spinal fluid, skin, vascular epithelium, oral epithelium, or chorionic villus.

138. (New) A method of identifying a human carrier of an heritable allele associated with spondyloepimetaphyseal dysplasia, comprising:

a) amplifying a nucleic acid segment from a sample of a bodily substance containing human nucleic acid, said sample being derived from a human subject without a symptom of spondyloepimetaphyseal dysplasia, said nucleic acid segment defining a sequence from human chromosomal region 10q23-24, between microsatellite markers D10S1143 and D10S2470, to produce amplification products; and

b) analyzing the amplification products for the presence of a variant allele of a gene encoding a PAPS synthetase, the presence of the variant allele of the gene identifying the human subject as a carrier of an heritable allele associated with spondyloepimetaphyseal dysplasia.

139. (New) The method of Claim 138, wherein the sample is of blood, hair root, urine, amniotic fluid, spinal fluid, skin, vascular epithelium, oral epithelium, or chorionic villus.

140. (New) The method of Claim 138, wherein an oligonucleotide primer is used to amplify the nucleic acid segment.

141. (New) The method of Claim 140, wherein the oligonucleotide primer has a nucleotide sequence of 5'-TGGACCAAGGATGACGATGT-3' (SEQ. ID. NO.:3), 5'-CGGAAAGATGGC AACAATGG-3' (SEQ. ID. NO.:4), a sequence complementary to either, a *PAPSS2*-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or more contiguous nucleotide positions of any of these at its 5' or 3' end, or a *PAPSS2*-specific fragment of any of these at least 15 nucleotides long.

142. (New) The method of Claim 140, wherein the oligonucleotide primer has a nucleotide sequence of 5'-CTGGTGCTGGAAAAACAACG-3' (SEQ. ID. NO.:5), 5'-

TGCGAATGGAGAA ATAAAGCTG-3' (SEQ. ID. NO.:6), a sequence complementary to either, a *PAPSS2*-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or more contiguous nucleotide positions of any of these at its 5' or 3' end, or a *PAPSS2*-specific fragment of any of these at least 15 nucleotides long.

143. (New) The method of Claim 139, wherein the variant allele is characteristic of spondyloepimetaphyseal dysplasia Pakistani-type.

144. (New) A method of identifying a human carrier of an heritable allele associated with spondyloepimetaphyseal dysplasia Pakistani-type, comprising:

a) amplifying a nucleic acid segment from a sample of a bodily substance containing human nucleic acid, said sample being derived from a human subject without a symptom of spondyloepimetaphyseal dysplasia Pakistani-type, said nucleic acid segment defining a sequence from human chromosomal region 10q23-24, between microsatellite markers D10S1143 and D10S2470, to produce amplification products; and

b) analyzing the amplification products for the presence of homozygosity for a variant allele of a gene encoding a PAPS synthetase, said variant allele defining a stop codon instead of a serine codon corresponding to amino acid residue 475 of SEQ. ID. NO.:7, the presence of the variant allele of the gene identifying the human subject as a carrier of an heritable allele associated with spondyloepimetaphyseal dysplasia Pakistani-type.

145. (New) The method of Claim 144, wherein the sample is blood, hair root, urine, amniotic fluid, spinal fluid, skin, vascular epithelium, oral epithelium, or chorionic villus.

146. (New) The method of Claim 144, wherein an oligonucleotide primer is used to amplify the nucleic acid segment.

147. (New) The method of Claim 146, wherein the oligonucleotide primer has a nucleotide sequence of 5'-TGGACCAAGGATGACGATGT-3' (SEQ. ID. NO.:3), 5'-CGGAAAGATGGC AACAATGG-3' (SEQ. ID. NO.:4), a sequence complementary to either, a *PAPSS2*-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or

more contiguous nucleotide positions of any of these at its 5' or 3' end, or a *PAPSS2*-specific fragment of any of these at least 15 nucleotides long.

148. (New) The method of Claim 146, wherein the oligonucleotide primer has a nucleotide sequence of 5'-CTGGTGCTGGAAAAACAACG-3' (SEQ. ID. NO.:5), 5'-TGCGAATGGAGAA ATAAAGCTG-3' (SEQ. ID. NO.:6), a sequence complementary to either, a *PAPSS2*-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or more contiguous nucleotide positions of any of these at its 5' or 3' end, or a *PAPSS2*-specific fragment of any of these at least 15 nucleotides long.

149. (New) The method of Claim 144, wherein analyzing the amplification products comprises digesting the amplification products with a *Hinc* II restriction endonuclease.

150. (New) The method of Claim 144, wherein the sample is of blood, hair root, urine, amniotic fluid, spinal fluid, skin, vascular epithelium, oral epithelium, or chorionic villus.

151. (New) A genetic testing kit for diagnosing SEMD in a human subject or for identifying a human carrier of SEMD, said kit comprising an oligonucleotide primer(s) comprising:

(A) a nucleotide sequence of (SEQ. ID. NO.:3), (SEQ. ID. NO.: 4), (SEQ. ID. NO.:5), (SEQ. ID. NO.:6), (SEQ. ID. NO.: 11), (SEQ. ID. NO.: 12), (SEQ. ID. NO.:13), (SEQ. ID. NO.:14), (SEQ. ID. NO.:15), (SEQ. ID, NO.:16), (SEQ. ID. NO.:17), (SEQ. ID. NO.:18), or (SEQ. ID. NO.:28);

(B) a nucleotide sequence complementary to (A);

(C) a *PAPSS2*-specific fragment of (A) or (B) at least 15 nucleotides long; or

(D) a *PAPSS2*-specific nucleotide sequence at least 15 nucleotides long and overlapping at 5 or more contiguous nucleotide positions any sequence of (A) or (B) at its 5' or 3' end; and

instructions for using the primer(s) in diagnosing SEMD in a human subject or for identifying a human carrier of SEMD.

152. (New) A genetic testing kit for diagnosing spondyloepimetaphyseal dysplasia in a human subject or for identifying a human carrier of spondyloepimetaphyseal dysplasia, comprising the pairs of oligonucleotide primers of Claim 30; and

instructions for using the primer(s) in diagnosing SEMD in a human subject or for identifying a human carrier of SEMD.

153. (New) A genetic testing kit for diagnosing spondyloepimetaphyseal dysplasia in a human subject, or for identifying a human carrier of spondyloepimetaphyseal dysplasia, comprising the pair of oligonucleotide primers of Claim 120; and

instructions for using the primer(s) in diagnosing SEMD in a human subject or for identifying a human carrier of SEMD.--.